Functional and transcriptional characterization of human embryonic stem cell-derived endothelial cells for treatment of myocardial infarction.

Journal: PLoS One

Publication Year: 2009

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PubMed link: 20046878

Funding Grants: In Vivo Imaging of Human Embryonic Stem Cell Derivatives and Tumorigenicity

Public Summary:
In this study, we developed an extracellular matrix culture system for increasing endothelial differentiation and ensuring animal free hESC-ECs. We designed a staged protocol that involved EB formation (stage 1) and expansion of endothelial lineage by subculturing EBs in collagen (stage 2). We then derive a highly pure endothelial population by CD31/CD144 double sorting using flow cytometry. In order to define at a molecular level the changes occurring at each stage of hESC differentiation to endothelial cell progeny, and to validate that these cells are similar to human umbilical vein endothelial cells (HUVECs), we also perform transcriptional profiling using whole human genome microarrays and real-time PCR arrays. Finally, to fully understand the beneficial effects of stem cell therapy, one must also be able to track the transplanted cells in living subjects over time in order to better understand their behavior and function in vivo. Therefore, we performed multi-modality imaging in a murine dorsal window model and a murine myocardial ischemia model to assess hESC-EC fate and function.

Scientific Abstract:
BACKGROUND: Differentiation of human embryonic stem cells into endothelial cells (hESC-ECs) has the potential to provide an unlimited source of cells for novel transplantation therapies of ischemic diseases by supporting angiogenesis and vasculogenesis. However, the endothelial differentiation efficiency of the conventional embryoid body (EB) method is low while the 2-dimensional method of co-culturing with mouse embryonic fibroblasts (MEFs) require animal product, both of which can limit the future clinical application of hESC-ECs. Moreover, to fully understand the beneficial effects of stem cell therapy, investigators must be able to track the functional biology and physiology of transplanted cells in living subjects over time. METHODOLOGY: In this study, we developed an extracellular matrix (ECM) culture system for increasing endothelial differentiation and free from contaminating animal cells. We investigated the transcriptional changes that occur during endothelial differentiation of hESCs using whole genome microarray, and compared to human umbilical vein endothelial cells (HUVECs). We also showed functional vascular formation by hESC-ECs in a mouse dorsal window model. Moreover, our study is the first so far to transplant hESC-ECs in a myocardial infarction model and monitor cell fate using molecular imaging methods. CONCLUSION: Taken together, we report a more efficient method for derivation of hESC-ECs that express appropriate patterns of endothelial genes, form functional vessels in vivo, and improve cardiac function. These studies suggest that hESC-ECs may provide a novel therapy for ischemic heart disease in the future.

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